PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P10828 PC	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/DK2004/000215	International filing date *(day/month/year)* 26.03.2004	Priority date *(day/month/year)* 26.03.2003
International Patent Classification (IPC) or national classification and IPC A61K9/22, A61K9/00		
Applicant EGALET A/S et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2005	04.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer von Eggelkraut-Gotta Telephone No. +31 70 340-4732

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000215

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-63	as originally filed
Claims, Numbers	
1-68	received on 09.04.2005 with letter of 07.04.2005
Drawings, Sheets	
1-22	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000215

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 64-68 with respect to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 64-68 with respect to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-68
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-68
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III.

1.
Claims 64-68 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V.

2.
For the assessment of the present claims 64-68 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3 INDEPENDENT CLAIM 1

3.1 The document **WO 95/22962** is regarded as being the closest prior art to the subject-matter of claim 1, and shows (the references in parentheses applying to this document):
A pharmaceutical composition for the zero order controlled release of at least one active substance into an aqueous medium by erosion of at least one surface of the composition, the composition comprising i) a matrix composition comprising a) a polymer or a mixture of polymers, b) an active substance and, optionally, c) one or more pharmaceutically acceptable excipients, and ii) a coating having at least one opening exposing at the one surface of said matrix, the coating comprising a) a first cellulose derivative which has thermoplastic properties and which is substantially insoluble in the aqueous medium in which the composition is to be used, and at least one of b) a second cellulose derivative which is soluble or dispersible in water, c) a

plasticizer, and d) a filler. The composition is in the form of rods. (p. 3, l. 4-28; p. 5, par. 2 - p. 14, par. 1; p. 16, par. 2; ex. 1,2; claims)

3.2 The subject-matter of claim 1 differs from this known composition in that the active agent is an opioid and in that the matrix composition has a conus-like shape, resulting in the zero-order release as claimed in claim 1.

3.3 The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

3.4 The problem to be solved by the present invention may be regarded as the provision of a composition for the zero order release of an opioid.

3.5 The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: **WO 95/22962** does not disclose or suggest a composition having a conus like shape resulting in the zero order release as claimed in claim 1.

3.6 For the same reasons independent claim 64 is also considered to be inventive.

3.7 Claims 2-63 and 65-68 are dependent on claim 1 and 64, respectively, and as such also meet the requirements of the PCT with respect to novelty and inventive step.

PCT/DK2004/000215 Egalet a/s
Morphine controlled release system

Amended set of claims in response to written opinion dated 9 July 2004

1. A pharmaceutical composition for controlled release of at least one opioid into an aqueous medium by erosion of at least one surface of the composition, the composition comprising

i) a matrix composition comprising a) a polymer or a mixture of polymers, b) an active substance and, optionally, c) one or more pharmaceutically acceptable excipients, and

ii) a coating having at least one opening exposing at the one surface of said matrix, the coating comprising

a) a first cellulose derivative which has thermoplastic properties and which is substantially insoluble in the aqueous medium in which the composition is to be used,

and at least one of

b) a second cellulose derivative which is soluble or dispersible in water,

c) a plasticizer, and

d) a filler,

wherein the matrix composition has a conus-like shape so that the surface area exposed to the aqueous medium increases at least during initial erosion of the matrix composition, and

the dissolution of the opioid - when tested in a Dissolution Test as described herein with or without application of sinkers - results in a zero order release of at least 80% of the opioid contained in the composition, and about 75% w/w of the opioid is released from the composition within 4-10 hours as measured by the dissolution test described herein.

2. A pharmaceutical composition according to claim 1, wherein the surface area exposed is increasing during the first 0.5 hours such as, e.g., during the first 1 hour,

during the first 1.5 hours, during the first 2 hours, during the first 3 hours, during the first 5 hours or during the first 6 hours.

3. A pharmaceutical composition according to claim 1 or 2, wherein the increase in surface area relates to an increase in diameter of the surface area of at least one exposed surface area upon erosion of that surface, and the ratio between the largest and smallest diameter is decreasing from about 2.5 to 1 during the erosion, such as from about 2 to 1, such as from as from about 1.8 to 1, such as from about 1.6 to 1, such as from as from about 1.5 to 1, such as from about 1.4 to 1 such as from about 1.3 to 1, such as from about 1.2 to 1.

4. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration 8 hours after oral administration to at least 6 healthy adult humans is at least 40% of the mean maximal concentration obtained by the dose, such as, e.g., at least 50% or at least 60% of the mean maximal concentration,

5. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration 10 hours after oral administration to at least 6 healthy adult humans is at least 35% of the mean maximal concentration obtained by the dose, such as, e.g., at least 40% or at least 50% of the mean maximal concentration.

6. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration 12 hours after oral administration to at least 6 healthy adult humans is at least 25% of the mean maximal concentration obtained by the dose, such as, e.g., at least 30%, at least 35% at least 40% or at least about 45% of the mean maximal concentration.

7. A pharmaceutical composition according to any of the preceding claims for administration once or twice daily.

8. A pharmaceutical composition according to any of the preceding claims for administration once daily.

9. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration after oral administration of a single dose to at least 6 healthy adult humans is at least 33% of the mean maximal concentration for at least 15 hours such as, e.g., for at least 17 hours, for at least 19 hours or for at least 20 hours.

10. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration after oral administration of a single dose to at least 6 healthy adult humans is at least 50% of the mean maximal concentration for at least 6 hours such as, e.g., for at least 8 hours, for at least 9 hours, for at least 10 hours or for at least 11 hours.

11. A pharmaceutical composition according to any of the preceding claims, wherein the mean plasma concentration after oral administration of a single dose to at least 6 healthy adult humans is at least 75% of the mean maximal concentration for at least 3 hours such as, e.g., for at least 3.3 hours, for at least 3.5 hours, for at least 3.7 hours or for at least 3.9 hours.

12. A pharmaceutical composition according to claim 8, wherein the mean plasma concentration 12 hours after oral administration of a single dose is at least 20% such as, e.g., at least 25% or at least 30% of the mean maximal concentration, and/or the mean plasma concentration 18 hours after oral administration is at least 20% such as, e.g., at least 25%, at least 30% or at least 35% of the mean maximal concentration, and/or the mean plasma concentration 24 hours after oral administration is at least 20% such as, e.g., at least 25% or at least about 30% of the mean maximal concentration.

13. A composition according to any of the preceding claims, wherein the opioid is selected from the group consisting of alfentanil, allylprodine, alphaprodine, aniloridine, benzylmorphine, bezitramide, buprenorphine, butophanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diapromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimephetanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol,

levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, morphine 6- glucuronide, morphine 3-glucuronide, myrophine, nalbuphine, narccine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, and pharmaceutically acceptable salts, complexes, solvates or anhydrates thereof, and mixtures thereof.

14. A composition according to any of the preceding claims, wherein the opioid is morphine, morphine 6- glucuronide, morphine 3-glucuronide or mixtures thereof.

15. A composition according to any of the preceding claims, wherein the active substance is a pharmaceutically active powder.

16. A composition according to claim 15, wherein the powder has a particle size of from about 0.1 μm to about 500 μm, typically from about 0.5 μm to about 300 μm, more typically from about 1 μm to about 200 μm, especially from about 5 μm to about 100 μm.

17. A composition according to any of the preceding claims, wherein the opioid is present in the matrix composition in a concentration of from about 0.1 to about 98% w/w such as, e.g. at the most about 90% w/w, at the most about 85% w/w, at the most about 80% w/w, at the most about 75% w/w, at the most about 70% w/w, at the most about 65% w/w or at the most about 60% w/w.

18. A composition according to any of the preceding claims, wherein about 50% w/w of the opioid is released from the composition within 3-5 hours as measured by the dissolution test described herein.

(original claim 19 inserted in claim 1).

19. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8 without sinkers) – releases at least about 80% w/w of the total amount of the opioid in a time period of from about 5 to about 10 hours

such as, e.g., from about 6 to about 9 hours such as e.g from about 7 to 8 hours or about 7.5 hours after start of the test.

20. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8 with sinkers) – releases at least about 80% w/w of the total amount of the opioid in a time period of from about 4 to about 9 hours such as, e.g., from about 5 to about 8 hours such as e.g from about 6 to 7 hours or about 6 hours after start of the test.

21. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8) – releases the opioid so that when 30% of the time to release at least about 80% w/w of the total amount of the opioid is reached - then from about 10% to about 50% such as, e.g., from about 15% to about 40% w/w, from about 20% to about 30% or about 23-27% w/w is released.

22. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8) – releases the opioid so that when 50% of the time to release at least about 80% w/w of the total amount of the opioid is reached - then from about 20% to about 60% w/w such as, e.g., from about 30% to about 50% w/w or about 42-47% w/w is released.

23. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8) – releases the opioid so that when 60% of the time to release at least about 80% w/w of the total amount of the opioid is reached - then from about 30% to about 80% w/w such as, e.g., from about 40% to about 70% w/w, from about 50 to about 60% or about 52-58% w/w is released.

24. A composition according to any of the preceding claims, wherein the composition – when tested in an *in vitro* dissolution system according to USP (paddle, 50 rpm, buffer pH 6.8) – releases the opioid in the following manner:

within the first 2 hours after start of the test from about 0 to about 30% w/w of the opioid is released,

within the first 5 hours after start of the test from about 25% to about 80% w/w of the opioid is released,

within the first 7 hours after start of the test from about 40% to about 100% w/w of the opioid is released.

25. A composition according to any of the preceding claims, wherein the composition has a dissolution pattern that resembles that of Figure 21 herein, the composition being tested under similar conditions.

26. A composition according to any of the preceding claims wherein the matrix composition has a shape selected from the shapes defined in Table A herein.

27. A composition according to claim 23, wherein the shape corresponds to cone 1 or 5 in Table A herein.

28. A composition according to any of the preceding claims, wherein the polymer is a substantially water soluble or crystalline polymer or a mixture of substantially water soluble and/or crystalline polymers.

29. A composition according to any of the preceding claims, wherein the polymer matrix comprises a polyglycol.

30. A composition according to any of the preceding claims, wherein the matrix comprises a homopolymer and/or a copolymer.

31. A composition according to any of the preceding claims, wherein the matrix comprises a polyethylene glycol, a polyethylene oxide and/or a block copolymer of ethylene oxide and propylene oxide including including poly(ethylene-glycol-b-(DL-lactic acid-co-glycolic acid) - b- ethylene glycol (PEG-PLGA PEG), poly((DL-lactic acid-co-glycolic acid) - g-ethylene glycol) (PLGA-g-PEG), and polyethylene oxide - polypropylene oxide (PEO-PPO).

32. A composition according to claim 31, wherein the polyethylene glycol, a polyethylene oxide and/or a block copolymer of ethylene oxide and propylene oxide has a molecular weight of from about 20,000 daltons, such as, e.g., from about 20,000 to about 700,000 daltons, from about 20,000 to about 600,000 daltons, from about 35,000 to about 500,000 daltons, from about 35,000 to about 400,000 daltons, from about 35,000 to about 300,000 daltons, from about 50,000 to about 300,000 daltons, such as, e.g. about 35,000 daltons, about 50,000 daltons, about 75,000 daltons, about 100,000 daltons, about 150,000 daltons, about 200,000 daltons, about 250,000 daltons, about 300,000 daltons or about 400,000 daltons.

33. A composition according to claim 31, wherein the block copolymer of ethylene oxide and propylene oxide comprises up to about 30% w/w of the propylene oxide based block, and has a molecular weight of about 5,000 daltons, typically about 5,000 to about 30,000 daltons such as, e.g. from about 8,000 to about 15,000 daltons.

34. A composition according to any of the preceding claims, wherein the matrix comprises a polymer which has a melting point of about 20-120°C such as, e.g. from about 30 to about 100°C or from about 40 to about 80°C.

35. A composition according to any of the preceding claims, wherein the polymer is a polyethylene oxide having a molecular weight of at least 100,000 daltons and at the most 300,000 daltons.

36. A composition according to any of the preceding claims, wherein the matrix composition comprises PEO 200,000 NF and/or PEO 200,000 LF.

37. A composition according to any of the preceding claims, wherein the matrix comprises a pharmaceutically acceptable excipient.

38. A composition according to any of the preceding claims, wherein the pharmaceutically acceptable excipient is selected from the group consisting of inorganic acids, inorganic bases, inorganic salts, organic acids or bases and pharmaceutically acceptable salts thereof, saccharides, oligosaccharides, polysaccharides, and cellulose and cellulose derivatives.

39. A composition according to claim 38, wherein the organic acid is a mono-, di-, oligo, polycarboxylic acid or amino acids such as, e.g. acetic acid, ethanoic acid, succinic acid, citric acid, tartaric acid, acrylic acid, benzoic acid, malic acid, maleic acid, adipic acid, angelic acid, ascorbic acid/vitamin C, carbamic acid, cinnamic acid, citramalic acid, formic acid, fumaric acid, gallic acid, gentisic acid, glutaconic acid, glutaric acid, glyceric acid, glycolic acid, glyoxylic acid, lactic acid, levulinic acid, malonic acid, mandelic acid, oxalic acid, oxamic acid, pimelic acid, pyruvic acid, aspartic and glutamic acid.

40. A composition according to claim 38, wherein the inorganic acid is pyrophosphoric, glycerophosphoric, phosphoric such as ortho or meta phosphoric, boric acid, hydrochloric acid, or sulfuric acid.

41. A composition according to claim 38, wherein the suitable inorganic compounds include aluminium.

42. A composition according to claim 38, wherein the suitable organic bases are selected from the group consisting of p-nitrophenol, succinimide, benzenesulfonamide, 2-hydroxy-2cyclohexenone, imidazole, pyrrole, diethanolamine, ethyleneamine,tris (hydroxymethyl) aminomethane, hydroxylamine and derivates of amines, sodium citrate, aniline, and hydrazine.

43. A composition according to claim 38, wherein the suitable inorganic bases are selected from the group consisting of aluminium oxide such as, e.g., aluminium oxide trihydrate, alumina, sodium hydroxide, potassium hydroxide, calcium carbonate, ammonium carbonate, ammnonium hydroxide, KOH and the like.

44. A composition according to claim 38, wherein the pharmaceutically acceptable salt of an organic acid is e.g. an alkali metal salt or an alkaline earth metal salt such as, e.g. sodium phosphate, sodium dihydrogenphosphate, disodium hydrogenphosphate etc., potassium phosphate, potassium dihydrogenphosphate, potassium hydrogenphosphate etc., calcium phosphate, dicalcium phosphate etc., sodium sulfate, potassium sulfate, calcium sulfate, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, potassium hydrogencarbonate, calcium carbonate, magnesium carbonate etc., sodium acetate, potassium acetate, calcium acetate, sodium succinate, potassium succinate, calcium succinate, sodium citrate,

potassium citrate, calcium citrate, sodium tartrate, potassium tartrate, calcium tartrate, zinc gluconate, zinc sulphate etc.

45. A composition according to claim 38, wherein the inorganic salt is sodium chloride, potassium chloride, calcium chloride, magnesium chloride etc.

46. A composition according to claim 38, wherein the pharmaceutically acceptable excipient is selected from glucose and other monosaccharides, ribose, arabinose, xylose, lyxose, allose, altrose, inosito, glucose, sorbitol, mannose, gulose, idose, galactose, talose, mannitol, fructose, lactose, sucrose; and other disaccharides, dextrin, dextran or other polysaccharides, amylose, xylan; cellulose and cellulose derivatives such as, e.g. microcrystalline cellulose, methyl cellulose, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxymethylpropyl cellulose, hydroxypropylmethyl cellulose, amylopectin, pectin, starch, sodium starch etc.,kaolin, bentonit, acacia, alginic acid, sodium alginate, calcium alginate, gelatin, dextrose, molasses, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husk, veegum, glycollate, magnesium stearate, calcium stearate, stearic acid, talc, titanium dioxide, silicium dioxide, clays, croscarmellose, gums, agar etc.

47. A composition according to any of the preceding claims further comprising a pharmaceutically acceptable excipient selected from the group consisting of fillers, diluents, disintegrants, glidants, pH-adjusting agents, viscosity adjusting agents, solubility increasing or decreasing agents, osmotically active agents and solvents.

48. A composition according to any of the preceding claims, wherein the at least one opioid has a solubility of at the most about 3 mg/ ml such as, e.g. at the most about 1 mg/ml, at the most about 0.1 mg/ml, at the most about 0.05 mg/ml such as, e.g. at the most about 0.001 mg/ml in water at ambient temperature.

49. A composition according to claim 45, wherein the matrix composition comprises a pharmaceutically acceptable excipient which has a solubility of at least 1 mg/ml such as, e.g. at least about 3 mg/ml, at least about 5 mg/ml, at least about 10 mg/ml, at least about 25 mg/ml or at least about 50mg/ml in water at ambient temperature.

50. A composition according to any of claims 1-47, wherein the at least one opioid has a solubility of at least about 3 mg/ml such as, e.g., at least about 5 mg/ml, at least about 10 mg/ml, at least about 20 mg/ml, at least about 50 mg/ml or at least about 100 mg/ml in water at ambient temperature.

51. A composition according to claim 50, wherein the matrix composition comprises a pharmaceutically acceptable excipient, which has a solubility of at the most about 3 mg/ml such as, e.g., at the most about 1 mg/ml, at the most about 0.1 mg/ml, at the most about 0.05 mg/ml such as, e.g. at the most about 0.001 mg/ml in water at ambient temperature.

52. A composition according to any of the preceding claims, wherein in the aqueous medium in which the composition is to be used, the coating does not completely crumble or erode before the matrix has completely eroded.

53. A composition according to any of the preceding claims, wherein said first cellulose derivative is a cellulose ether which, when heated, is shapeable by molding or extrusion, including injection molding, blow molding and compression molding.

54. A composition according to claim 53 in which the cellulose ether comprises at least one ethylcellulose.

55. A composition according to any of claims 1-52 in which said first cellulose derivative is selected from the group consisting of cellulose acetate, cellulose propionate and cellulose nitrate.

56. A composition according to any of the preceding claims in which said second cellulose derivative is selected from the group consisting of methylcellulose, carboxymethylcellulose and salts thereof, cellulose acetate phthalate, microcrystalline cellulose, ethylhydroxyethylcellulose, ethylmethylcellulose, hydrocyethylcellylose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose and hydroxymethylpropylcellulose.

57. A composition according to claim 56 in which said salt of carboxymethylcelllulose is selected from the group consisting of alkali metal and alkaline earth metal salts.

58. A composition according to any of the preceding claims, in which said plasticizer is selected from the group consisting of phosphate esters; phthalate esters; amides; mineral oils; fatty acids and esters thereof with polyethylene glycol, glycerin or sugars; fatty alcohols and ethers thereof with polyethylene glycol, glycerin or sugars; vegetable oils and hydrogenated vegetable oils; nitrobenzene, carbon disulfide, β-naphtyl salicylate, phthalyl glycolate, and diocyl phthalate.

59. A composition according to claim 58 in which said fatty alcohol is selected from the group consisting of cetostearyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol and myristyl alcohol.

60. A composition according to any of the preceding claims in which said plasticizer is a non-ionic surfactant.

61. A composition according to any of the preceding claims, wherein the matrix composition does not contain polyethylene glycol 2000 monostearate or polyethylene glycol 400 monostearate.A composition according to any of the preceding claims, wherein the pharmaceutically acceptable excipient is present and is selected from mannitol, xylitol, sorbitol and inositol.

62. A composition according to any of claims 1-61, wherein the pharmaceutically acceptable excipient is an aluminium oxide

63. A composition according to any of the preceding claims, wherein comprising PEO 200,000 as polymer and mannitol and/or aluminium oxide as pharmaceutically acceptable excipient.

64. A method for treating a patient suffering from pain sensible to an opioid comprising administering such opioid in a composition according to any of claims 1-63.

65. A method according to claim 64, wherein the amount of opioid on a daily basis sufficient to threat the pain in the patient is less than the amount of opioid sufficient to treat the pain to a similar degree by use of an immediate release composition.

66. A method according to claim 65, wherein the degree of pain treatment is measured by use of a 4 point verbal rating scale (VRSpi) where 0=none pain, 1=slight pain 2=moderate pain, 3=severe pain.

67. A method according to claim 64 wherein the treatment is associated with less side effects compared to a treatment with a similar amount of opioid in an immediate release composition.

68. A method according to claim 67 where the side effects is selected from the group consisting of sedation, nausea, dizziness, vertigo, obstipation, urine retention, itching, perspiration, dry mouth, break trough pain etc.